Anthocyanins as a Potential Natural Antidiabetic

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Diabetes mellitus (DM) is a metabolic disease characterized by abnormal blood glucose levels-hyperglycemia, caused by a lack of insulin secretion, impaired insulin action, or a combination of both. The incidence of DM is increasing, resulting in billions of dollars in annual healthcare costs worldwide. Therapeutics aim to control hyperglycemia and reduce blood glucose levels to normal. However, most modern drugs have numerous side effects, some of which cause severe kidney and liver problems. On the other hand, natural compounds rich in anthocyanidins (cyanidin, delphinidin, malvidin, pelargonidin, peonidin, and petunidin) have also been used for the prevention and treatment of DM.

Keywords: diabetes mellitus ; bioactive compounds ; anthocyanins

1. Introduction

The main sources of phenolic compounds include plants, fruits, and vegetables. The primary classes of phenolics are flavonoids and non-flavonoids, and they have already been demonstrated to have bioactive effects against a variety of diseases [1]. These phytochemicals are promising agents to be used in the pharmaceutical, cosmetic, and food industries due to the variety of their chemical structures [2][3]. Flavonoids have been emphasized as phenolic substances with significant biological activities [4][5][6][7]. They are low-molecular-mass phenolic secondary compounds of plants that aid in defending plants from environmental stresses [8]. Additionally, flavonoids are recognized as floral pigments [9]. These compounds are made of two aromatic rings (A and B) and a heterocyclic ring (C) with an oxygen atom, each with a 15-carbon skeleton (C_6-C_3-C_6) [10].

Phenolic substances are well known for having properties that support health, such as antioxidant, antidiabetic, antimicrobial, anticancer, and others [3][11][12][13]. Anthocyanins have been shown to play a significant part in the process of metabolic diseases such as diabetes mellitus (DM) [14], with epidemiological research demonstrating an inverse relationship between dietary flavonoids and type 2 diabetes mellitus (T2DM) incidence [15][16][17].

2. Structure and Function

The family of flavonoids known as anthocyanidins and their glucosides, also known as anthocyanins (*anthos* means flower and *kyanos* means blue), produced via the phenylpropanoid pathway, are what give many fruits, vegetables, and beverages their deep red, purple, and blue colors [18]. They contribute to the nutritional and sensory properties of plants and are water-soluble [10]. These compounds may also function as pollinators, antifeedants, and phytoalexins, in addition to aiding in a plant's defense against pathogens, predators, UV radiation, and environmental factors [10]. Blueberries, cherries, raspberries, strawberries, purple grapes, black currants, and red wine are the main sources of anthocyanidins [18].

Chemically speaking, anthocyanins are found as a glycoside that contains both a non-sugar component (aglycone: anthocyanidin) and sugar (glycone moiety: glucose, galactose, xylose, rhamnose, or arabinose) [19]. These substances are flavonoids because they have three benzoic rings: an A ring, a heterocyclic ring with an oxygen atom (C ring), and a B ring that is benzoic with a carbon-carbon bond link called flavylium ion [20]—**Figure 1**.

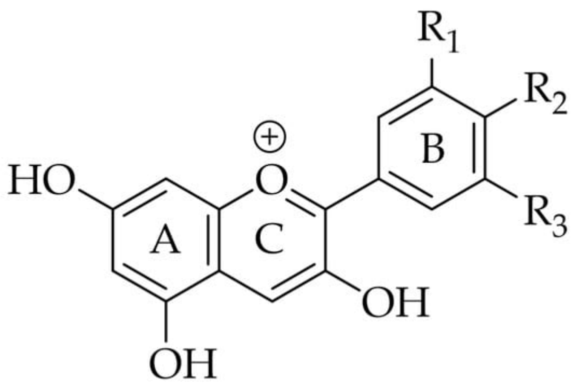

Figure 1. Chemical structure of anthocyanins: two benzoic rings (A) and (B) separated by a heterocyclic (C) ring.

The most prevalent anthocyanidins discovered in food are cyanidin, delphinidin, malvidin, pelargonidin, peonidin, and petunidin—**Table 1**, which are among the approximately 30 anthocyanidins currently known [10][21]. The classification of anthocyanins is made according to (i) the number, position, and degree of methylation of the hydroxyl groups; (ii) the number and nature of the sugar moieties bonded to the aglycone; and (iii) the position of the aliphatic and/or aromatic carboxylate acids on the sugar molecule [10]. Some of the elements accountable for the various biological activities of these compounds include hydroxylation, methylation, and the number and type of sugars linked to the aglycone [10][19][22]. Anthocyanins are powerful antioxidants because of their chemical structure. The anthocyanin skeleton's hydroxyl (-OH) and methoxy (-OCH_3) group count and location both have an impact on the antioxidant potential of the substance. For instance, the antioxidant activity is greater when there are more hydroxyl groups [10]. Additionally, cyanidin, delphinidin, and pelargonidin are highly effective against the superoxide anion, while pelargonidin is effective against hydroxyl radicals [23].

Table 1. Chemical structures and sources of six common anthocyanidins found in nature [23].

Anthocyanidin	R1	R2	R3	Natural Sources
Cyanidin	-OH	-OH	-H	Apple, blackberry, elderberry, plum, peach, nectarine
Delphinidin	-OH	-OH	-OH	Oranges, grapes, beans
Pelargonidin	-H	-OH	-H	Strawberries, red radishes
Malvidin	-OCH_3	-OH	-OCH_3	Grapes
Peonidin	-OCH_3	-OH	-H	Cranberries, blueberries, plums, cherries, grapes, purple corn
Petunidin	-OH	-OH	-OCH_3	Grapes, red berries

Anthocyanins are less stable due to factors such as temperature variations, cooking, exposure to light and oxygen, as well as the presence of enzymes, phenolic compounds, metal ions, ascorbic acid, hydrogen peroxide, and water [24]. They are also influenced by storage and processing conditions.

3. Main Sources

Anthocyanins can be found in large amounts in many red and blue fruits and vegetables—**Table 1**. Their content depends on the species, cultivar, growing region, climate (e.g., temperature, humidity, light exposure), harvesting, ripening, processing, and storage conditions [18]. The main sources of anthocyanins are berries, like strawberries, blueberries, blackberries, blackcurrant, and raspberries [18]. These berries contain between 100 and 700 mg of anthocyanins per g of fresh fruit [25][26]. Elderberries and chokeberries have the greatest concentrations of these compounds (1.4 to 1.8 g per 100 g). The skin of cherries has the highest concentration of anthocyanins, followed by flesh and pits [27]. Other great sources include açai, purple corn, plums, pomegranates, eggplant, wine, grapes, and red/purple vegetables [25][26][28].

The Mediterranean diet, which is high in these phenolic compounds due to its abundance in red fruits and wine, is the one with the greatest daily intake of anthocyanins [29]. About 70% of the anthocyanins consumed every day come from fruits, while 25% come from wine 25% [30]. The main anthocyanidins consumed by humans are cyanidin, delphinidin, malvidin, pelargonidin, peonidin, and petunidin, with cyanidin 3-*O*-glucoside being primarily found in berries, and malvidin 3-*O*-glucoside in broad varieties of foods [18]. To guarantee an adequate level of bioactive compounds with health-promoting properties, regular consumption of fruits and vegetables is imperative. Numerous studies have shown that eating foods high in phenolic compounds, such as anthocyanins, can reduce oxidative stress and inflammation, which lowers the chance of developing chronic diseases [3][10][13][29].

4. Antidiabetic Potential

Anthocyanins have been found to be beneficial in the prevention and treatment of DM and its complications, according to several investigations [11][31][32]—**Table 2**. These compounds have demonstrated the ability to reduce hyperglycemia, insulin resistance, reactive species, and proinflammatory cytokines in this setting [5][11][15][31]. Additionally, they were found to be involved in gluconeogenesis suppression, as well as α-amylase and α-glucosidase activity [33][34][35].

The enzymes α-amylase and α-glucosidase hydrolyze carbohydrates and produce glucose, and thus they are crucial for controlling digestion and absorbing glucose. Numerous studies have demonstrated the ability of anthocyanins or the consumption of foods high in anthocyanins to inhibit these enzymes, thereby modulating postprandial blood glucose and preventing the onset of DM [5][33][35][36]. The α-glucosidase enzyme can be inhibited by sweet cherry extracts, according to previous research [5]. The authors claim that cherries are extremely rich in anthocyanins, especially cyanidin 3-*O*-rutinoside [5], which has already been shown to significantly inhibit α-glucosidase activity in a concentration-dependent way [37]. According to additional research, cyanidin from *Cinnamomum camphora* fruit inhibited α-glucosidase action more potently than Acarbose (a drug used for the management of glycemic control in patients with T2DM) [38]. The ability to inhibit α-glucosidase was also demonstrated in other experiments with blueberry, blackcurrant, and blue honeysuckle [39], blackberry [40], and bilberry and cranberry [41]. The activity of pancreatic α-amylase was shown to be inhibited by cyanidin-3-rutinoside in research conducted by Akkarachiyasit and colleagues [42]. According to recent research on animal studies, T2DM mice fed blackcurrant extract, which contains high levels of delphinidin 3-rutinoside, demonstrated a reduction in blood glucose concentration and an improvement in glucose tolerance [43]. Another study found that cyanidin 3-glucoside reduced fasting blood glucose and increased glycogen synthesis, which was most likely caused by an increase in GLUT-1 expression in the liver of *db/db* mice [44]. Malvidin, malvidin 3-glucoside, and malvidin 3-galactoside, which are all components of blueberry anthocyanin extract, were discovered by Herrera-Balandrano and co-works [45] to be capable of inhibiting diabetes hyperlipidemia and decrease insulin levels. In streptozotocin-induced diabetic rats treated for 12 weeks, anthocyanins from purple sweet potatoes improved blood glucose and lipid levels and reduced oxidative stress and liver damage [46].

In human studies, anthocyanins' ability to treat diabetes was also assessed. A randomized controlled study performed on 37 people with T2DM demonstrated that taking 350 mg of whortleberry fruit hydroalcoholic extract, every eight hours for two months could lower blood levels of fasting glucose, 2-h postprandial glucose, and HbA1C [47]. Similarly, eating freeze-dried strawberries for six weeks increased antioxidant capacity and blood glucose levels, while lowering inflammatory reaction and lipid peroxidation [48]. Anthocyanin supplementation for 12 weeks improved serum adiponectin and fasting glucose in patients with recently diagnosed diabetes, according to a study that included people with prediabetes or diabetes [49].

Despite a number of scientific studies showing that anthocyanins are crucial for the prevention and treatment of DM and its complications—**Table 2**, it is important to take into account that the limited bioavailability and poor stability of these colored compounds hinder the achievement of their highest therapeutic potential. To improve the efficacy of anthocyanins, lipids, polysaccharides, and protein complexes or nanoencapsulation may be suitable substitutes.

Table 2. In vitro studies, animal studies, and clinical trials on the antidiabetic potential of anthocyanins.

Source	Anthocyanin Type	Main Outcomes	Reference
Sweet Cherries (*Prunus avium* L.)	Anthocyanins-enriched fraction	α-glucosidase inhibition	[5]

Source	Anthocyanin Type	Main Outcomes	Reference
Cinnamomum camphora L. fruit	Cyanidin	α-glucosidase inhibition	[38]
Blueberry, blackcurrant and blue honeysuckle fruits	Anthocyanins-enriched fraction	α-glucosidase inhibition	[39]
Blueberries (*Vaccinium corymbosum*) and blackberries (*Rubus* spp.)	Anthocyanins-enriched fraction	α-glucosidase inhibition	[40]
Vaccinium oxycoccos L. and *Vaccinium myrtillus* L.	Anthocyanins-enriched fraction	α-glucosidase inhibition	[41]
n.d.	Cyanidin 3-rutinoside	α-amylase inhibition ↓ postprandial glycemia	[42]
Blackcurrant extract (11 g per kg)	Anthocyanins-enriched fraction	↓ blood glucose ↑ glucose tolerance	[43]
n.d.	Cyanidin 3-*O*-glucoside	↓ fasting blood glucose levels ↓ accumulation of liver lipids ↑ glycogen synthesis	[44]
Blueberry anthocyanin extract (100.4 mg per kg)	Anthocyanins-enriched fraction	↓ fasting blood glucose levels ↓ insulin levels ↑ liver antioxidants	[45]
Purple sweet potato	Anthocyanins-enriched fraction	↓ blood glucose levels ↑ glucose tolerance ↓ liver damage ↑ antioxidant capacity	[46]
Whortleberry fruit hydroalcoholic extract (1.0 g per day)	Anthocyanins-enriched fraction	↓ blood glucose of fasting glucose	[47]
Freeze-dried strawberry (100 g per day)	Anthocyanins-enriched fraction	↓ lipid peroxidation ↓ HbA1c and total antioxidant status	[48]

Source	Anthocyanin Type	Main Outcomes	Reference
n.d.	Anthocyanins (320 mg per day)	↑ adiponectin ↓ fasting glucose ↓ basal glycemia and insulinemia	[49]

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